REMARKS

Summary of Office Action

Claims 117-119, 134-139, 166, 167, and 175-179 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Fanara et al., U.S. Patent No. 6,699,502 (hereafter "FANARA").

Claims 120-123, 128-133, 140-153, 155-157, 159-165, 168-174, 180-195, and 198-200 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over FANARA in view of Jaeger, U.S. Patent No. 3,914,425 (hereafter "JAEGER").

Claims 124-127, 154, 158, 196 and 197 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over FANARA in view of JAEGER and further in view of Findlay et al., U.S. Patent No. 4,650,807 (hereafter "FINDLAY").

Claims 117-200 remain provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable of claims of one or more of co-pending application Nos. 10/736,902, 10/939,351, 11/012,267, 11/115,293 and 11/115,321.

Response to Office Action

Reconsideration and withdrawal of the rejections of record are again respectfully requested, in view of the following remarks.

Response to Rejection of Claims under 35 U.S.C. § 103(a) over FANARA alone

Claims 117-119, 134-139, 166, 167, and 175-179 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over FANARA. The rejection reiterates the allegations set

forth in the previous Office Action. In particular, the rejection again mainly relies on col. 2, lines 36-50 of FANARA where it allegedly is taught to simultaneously administer more than one active substance and combining the therapeutic effects of active substances with different pharmacokinetic profiles. The rejection again asserts that "[i]n order to have the combined therapeutic effects of active substances, it would have been obvious to one with ordinary skill in the art that the period of therapeutic effectiveness of the first active substance would be coextensive with the period of therapeutic effectiveness of the second active substance, especially if the two active substances are related to similar (antitussive) therapeutic activities."

Applicants respectfully traverse this rejection for the reasons set forth in the Appeal Brief filed October 20, 2008, the Reply Brief filed August 25, 2009, and the response to the previous Office Action. The corresponding remarks are expressly incorporated herein.

It further is noted again that the passage of FANARA which the Examiner appears to primarily rely on, i.e., col. 2, lines 36-50, states (emphasis added):

> In parallel, it is increasingly therapeutically advantageous to be able to simultaneously administer by the oral route an active substance released immediately after administration, and the same or a second active substance released gradually and regularly after administration. In the case where the same active substance is simultaneously administered for immediate release and for prolonged release, this makes it possible to rapidly release a sufficient dose of active substance to trigger the desired effect and to maintain this effect by a gradual and prolonged release of the same active substance. In the case where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles.

It is submitted again that FANARA does not explain what exactly is to be understood by the phrase "very different pharmacokinetic profiles" and it is only with hindsight that one can interpret this passage to suggest to one of ordinary skill in to art to provide a dosage form which comprises two different active substances (having different half-lives), one released immediately after administration and the other one released gradually and continously after administration,

and releases the two active substances in such a manner that the plasma concentration of one active substance is within a therapeutic range over a period which is coextensive with at least about 70 % of the period over which the plasma concentration of the other active substance is within a therapeutic range.

In this regard, it further is submitted that the last sentence of the above passage must not be read in isolation but within the entire context of this passage and in particular, in the context of the preceding sentence (underlined). In particular, the preceding sentence is concerned with the scenario where there is a need for fast action of a particular drug, i.e., to get the plasma concentration of the drug into the therapeutic range as fast as possible in order to treat or alleviate the condition or symptom to be treated as fast as possible (accomplished by an immediate release composition) and to thereafter maintain a concentration of this (the same) drug within the therapeutic range for prolonged periods of time (accomplished by a sustained release composition).

The equivalent of this scenario when two drugs "having very different pharmacokinetic profiles" are used in a single dosage form would, for example, be the use a first drug that is suitable for rapidly alleviating the symptoms of a condition due to the fact that it can rapidly be absorbed by the body and can rapidly afford a plasma concentration within the therapeutic range (e.g., a decongestant) and is provided in an immediate release composition (i.e., the entire first drug is released at once), followed by the sustained release of a second drug that treats the cause of the condition (e.g., an antihistamine) but takes more time to be absorbed by the body and thus, is not suitable for providing rapid relief from the symptoms of the condition. It is apparent that with this scenario there is no need for any overlap between the periods of a plasma concentration within the respective therapeutic ranges of the rapidly acting first drug and the second drug

because once the second drug treats the cause of the condition the symptoms thereof will disappear and there is no longer a need to alleviate these symptoms with the first drug. In other words, the period of a therapeutic plasma concentration of the first drug needs to last only up to the time when the second drug has reached its therapeutic plasma concentration. Clearly, a significant overlap of these two periods would not serve any useful purpose at all.

A second, similar scenario in which two drugs "having very different pharmacokinetic profiles" are used in a single dosage form is the case where both the first and the second drug are suitable for treating or alleviating the same condition (having the same therapeutic effect), the first drug being fast acting (rapidly absorbed) but having a relatively short half-life (thereby requiring large amounts of drug for maintaining its therapeutic effect for extended periods of time) and the second drug being slowly absorbed by the body but having a relatively long half-life, thereby requiring only relatively small amounts of drug to be continuously released once a plasma concentration within the therapeutic range is reached. In this case too, there apparently is no need for any significant overlap between the periods of a therapeutic plasma concentration of the first drug and the second drug.

It additionally is submitted that the above-cited passage of FANARA must also be considered and assessed in the context of the entire disclosure of FANARA.

For example, in lines 15-27 of col. 3 thereof FANARA makes it clear that the contribution to the art disclosed therein does not reside in the provision of dosage forms which provide immediate/controlled release of two different active substances but rather that the disclosed invention consists in the provision of a new matrix composition for the controlled release part of corresponding dosage forms (and, primarily, for dosage forms which consist of only a single, controlled release composition), which matrix composition has

certain advantages. Accordingly, one of ordinary skill in the art will understand that FANARA neither teaches nor suggests combined immediate/controlled release dosage forms which are different from the known dosage forms in any respect other than the composition of the matrix for the controlled release portion thereof.

Applicants further point out that the Examiner has failed to provide any (written or other) evidence which shows that differences in release rates of different active substances from a single dosage form result in and/or are conventionally used to provide plasma concentrations in a therapeutic range of two active substances (with different plasma half-lives) present in the single dosage form over similar or substantially coextensive periods of time. In fact, the Examiner has not even cited to a single example of the use of different release rates (and in particular, a combination of immediate release and controlled release) for achieving similar or substantially coextensive periods of therapeutic activity of two different active substances, let alone of two different active substances which comprise a morphine derivative having antitussive activity and an active substance whose half-life differs from that of the morphine derivative.

Further, instant claim 117, for example, recites generally a combination of elements, *inter alia*,

(1) a pharmaceutical dosage form which comprises a first drug which comprises at least one morphine derivative having antitussive activity and at least one second drug (selected, e.g., from decongestants, expectorants, mucus thinning drugs, and antihistamines);

(2) a difference in the plasma half-lives of the first and second drugs; and

(3) an overlap of the periods within which the first drug and the at least one second drug show a therapeutic effect (i.e., an overlap of the periods within which the first drug and the at least one second drug provide a plasma concentration with the respective

therapeutic ranges) of at least about 70 % (and up to at least about 95 %, see, e.g., claim 133).

In contrast, FANARA does not mention elements (2) and (3) at all and mentions element (1) merely in passing. Regarding elements (2) and (3) the rejection relies primarily on the general statement in col. 2, lines 36-50 of FANARA reproduced at page 3 of this Response.

The rejection essentially asserts that in view of the above statement in combination with the Examples of FANARA an in particular, Example 7 thereof (describing a double-layer tablet containing hydrocodone in both a controlled-release layer and an immediate release layer) it would have been obvious to one of ordinary skill in the art to provide a pharmaceutical dosage form which shows the combination of elements (1) to (3) set forth above. However, nothing in the above passages (or any other passage) of FANARA points to a dosage form which provides a plasma concentration within a therapeutic range of a first active substance and a plasma concentration within a therapeutic range of a second active substance over similar or substantially coextensive periods of time, respectively, let alone in a case where the plasma half-lives of these active substances are different.

Specifically, FANARA mentions exclusively immediate release/controlled release combinations, i.e., combinations which provide different release rates of the active substances (in this regard, see also Table 10 in col. 10 of FANARA which lists the time-dependent release of the drugs in the double-layer tablet of Example 4), but is completely silent with respect to the duration of action of the active substances, let alone the duration of action of one drug in relation to the duration of action of the other drug.

In this regard, Applicants point out that "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or

why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Labs.*, 512, F.3d 1363, 1374 n.3 (Fed. Cir. 2008). "[I]t is not enough to simply show that the references disclose the claim limitations; in addition, 'it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does.'" *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617, F.3d 1296, 1303 (Fed. Cir. 2010). Further, it is also necessary for the Examiner to properly construe what an applied reference *fairly* teaches or discloses. See, e.g., *In re Fracalossi and Wajer*, 681 F.2d 792 (CCPA 1982). Ultimately therefore, "[i]n determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir 1995) (internal quotations omitted).

Further, regarding the allegations and the graphs provided at page 7 of the instant Office Action, it is not clear to Applicants why the alleged different possible interpretations of claim 117 make any difference in the instant context. Clarification in this regard is respectfully requested. If the Examiner is of the opinion that claim 117 is indefinite the Examiner should have rejected claim 117 under 35 U.S.C. § 112, second paragraph, not under 35 U.S.C. § 103(a).

It further is submitted that these graphs and the accompanying allegations appear to be an indication that the Examiner has not completely understood the meaning and implications of the rejected claims. At any rate, these graphs and allegations even further illustrate the non-obviousness of the subject matter of the rejected claims.

For example, according to graph A ("Co-extensive plasma concentration) there is a measurable plasma concentration for both drugs over the same time period, i.e., from time 0 to time 8. In other words, there is a 100 % overlap in the time periods over which these two drugs

show a measurable plasma concentration. However, this overlap does not mean that there also is a 100 % overlap in the periods over which the drugs show plasma concentrations within the therapeutic ranges thereof.

In particular, if one were to assume, for example, that the minimum plasma concentration at which the first drug shows a therapeutic effect is 10, the plasma concentration within the therapeutic range for the first drug would be from time 1 to time 7, i.e., would span 6 time units. If one further were to assume that the minimum plasma concentration at which the second drug shows a therapeutic effect is 15, the plasma concentration within the therapeutic range for the second drug would be from time 2.5 to time 5.5, i.e., would span only 3 time units. Accordingly, despite the fact that both drugs show a 100 % overlap in the time periods over which their plasma concentrations are measurable, in this case the period over which the plasma concentration of the second drug is within the therapeutic range would be coextensive with only 50 % of the period over which the plasma concentration of the first drug is within the therapeutic range.

Accordingly, even if one of ordinary skill in the art were to select suitable formulations for two different drugs to ensure that both drugs, when ingested together, are present in a patient's plasma over substantially the same period, this would by no means guarantee that the periods over which these drugs show plasma concentrations within their therapeutic ranges overlap to a significant extent (as indicated in the rejected claims).

The above remarks should have made it apparent that the concept on which the present invention is based is much more sophisticated than is appreciated by the Examiner.

Applicants submit that for at least the foregoing reasons and the additional reasons set forth in the Appeal Brief filed October 20, 2008, the Reply Brief filed August 25, 2009 and the

response to the previous Office Action the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of any of the claims of record in view of FANARA. Accordingly, the rejection of claims 117-119, 134-139, 166, 167, and 175-179 under 35 U.S.C. § 103(a) over FANARA is without merit and should be withdrawn, which action is again respectfully requested.

Response to Rejection of Claims under 35 U.S.C. § 103(a) over FANARA in View of JAEGER and FINDLAY

Claims 120-123, 128-133, 140-153, 155-157, 159-165, 168-174, 180-195, and 198-200 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over FANARA in view of JAEGER and claims 124-127, 154, 158, 196 and 197 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over FANARA in view of JAEGER and further in view of FINDLAY. The rejections reiterate the allegations set forth in the previous Office Action and appear to concede that FANARA alone does not render obvious the subject matter of the rejected claims but allege that JAEGER or JAEGER and FINDLAY, respectively cure the deficiencies of FANARA in this regard.

These rejections are respectfully traversed as well, for the reasons set forth in the response to the previous Office Action. The corresponding remarks are expressly incorporated herein.

Applicants submit that it is not seen that JAEGER and FINDLAY are able to cure any of the deficiencies of FANARA set forth above, and neither has the Examiner offered any explanation in this regard. For example, neither FANARA nor JAEGER mentions differences in half-lives of two drugs, let alone teaches or suggests that two drugs whose half-lives differ significantly (e.g., by at least about 2 hours) should be combined in a way such that their periods

of therapeutic effectiveness are substantially coextensive.

Regarding the allegations at page 14, second paragraph of the instant Office Action, Applicants point out that the question here is not whether or not the half-life of a drug "can be determined during the process of routine experimentation", but rather is whether FANARA in combination with JAEGER and FINDLAY renders it obvious to one of ordinary skill in the art to provide a dosage form wherein drugs having different half-lives (one of which being a morphine derivative having antitussive activity) are combined in such a manner that there is a substantial overlap in the periods of the therapeutic effectiveness of these drugs.

In view of the foregoing, the request to withdraw the rejections under 35 U.S.C. § 103(a) over the combined disclosures of FANARA, JAEGER and FINDLAY is respectfully maintained.

Response to Provisional Rejection of Claims on the Ground of Non-Statutory Obviousness-Type Double Patenting

All claims of record remain provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable of claims of one or more of co-pending application Nos. 10/736,902, 10/939,351, 11/012,267, 11/115,293 and 11/115,321.

Applicants respectfully again request that these rejections be held in abeyance until the Examiner has indicated allowable subject matter. Applicants will then decide if the filing of one or more Terminal Disclaimers is warranted.

CONCLUSION

In view of the foregoing, it still is believed that all of the claims in this application are in condition for allowance, which action is again respectfully requested. If any issues yet remain which can be resolved by a telephone conference, the Examiner is respectfully invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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Date

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